### **Supplementary Material**

#### Methods

#### Inclusion Criteria

We followed *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines in this systematic review to include all studies that evaluated patients with brain imaging (PET, SPECT, structural MRI, diffusion-weighted MRI, functional MRI) before and after courses of treatment for OCD (i.e., pharmacotherapy, cognitive behavioral therapy [CBT], stereotactic lesions, deep brain stimulation [DBS], or transcranial magnetic stimulation [TMS]). Patient groups included adults, children, treatment naïve, and treatment refractory groups. We included studies written in English. Studies published prior to 1990 were excluded due to variability in imaging parameters.

# Identification of Studies

We performed a literature search on PubMed using the Cochrane Collaboration search strategy.[S14] Search terms included: obsessive-compulsive disorder, OCD, positron emission tomography, PET, SPECT, HMPAO, diffusion tensor imaging, DTI, functional MRI, fMRI, imaging, voxel-based morphometry, VBM, volumetric MRI, resting state, SSRI, SRI, paroxetine, citalopram, clomipramine, fluoxetine, cognitive behavioral therapy, CBT, deep brain stimulation, DBS, cingulotomy, anterior capsulotomy, limbic leucotomy, subcaudate tractotomy, SCT, transcranial magnetic stimulation, and TMS. This search strategy was supplemented by a hand-search of bibliographies from studies that fit inclusion criteria. Studies were identified in April 2020.

#### Data Collection and Endpoints

For each study, data were recorded for treatment type, dosing (if applicable), imaging modality, number of subjects, age of subjects, past treatments, and pre- versus post-treatment imaging change. Imaging change was recorded based on imaging type and whether there was an increase, decrease, or no change of the parameter in question when comparing post-intervention imaging to pre-intervention imaging. Only changes that were statistically significant were included in the final analysis. Regions of interest (ROI) were defined based on specificity provided in the

studies reviewed; Brodmann areas (BA) were identified when possible. Imaging changes that significantly correlated with changes in symptom severity (e.g., change in Yale-Brown Obsessive-Compulsive Scale [Y-BOCS] scores)[S15-S16] are highlighted to emphasize that not all imaging changes correlated with symptom improvement. The Y-BOCS is a common symptom scale used to measure the severity of OCD symptoms, and a score greater than 24 typically defines severe OCD. A reduction of 35% or more in the score is commonly used to categorize a clinically significant treatment response.[S16]

# Cross-Treatment Analysis

Fluorodeoxyglucose (FDG) PET studies were aggregated and compared using weighted histograms. PET studies were represented this way because it was the most consistently used imaging modality across treatments.

# **Supplementary References**

- S1. Marsh, R., T.V. Maia, and B.S. Peterson, *Functional disturbances within frontostriatal circuits across multiple childhood psychopathologies*. Am J Psychiatry, 2009. **166**(6): p. 664-74.
- S2. Milad, M.R. and S.L. Rauch, *Obsessive-compulsive disorder: beyond segregated cortico-striatal pathways*. Trends Cogn Sci, 2012. **16**(1): p. 43-51.
- S3. Saxena, S. and S.L. Rauch, Functional neuroimaging and the neuroanatomy of obsessive-compulsive disorder. Psychiatr Clin North Am, 2000. **23**(3): p. 563-86.
- S4. Ahmari, S.E. and D.D. Dougherty, *Dissecting Ocd Circuits: From Animal Models to Targeted Treatments*. Depress Anxiety, 2015. **32**(8): p. 550-62.
- S5. Chamberlain, S.R., et al., *The neuropsychology of obsessive compulsive disorder: the importance of failures in cognitive and behavioural inhibition as candidate endophenotypic markers.* Neurosci Biobehav Rev, 2005. **29**(3): p. 399-419.

- S6. Gehring, W.J., J. Himle, and L.G. Nisenson, *Action-monitoring dysfunction in obsessive-compulsive disorder*. Psychol Sci, 2000. **11**(1): p. 1-6.
- S7. Sheth, S.A., et al., *Human dorsal anterior cingulate cortex neurons mediate ongoing behavioural adaptation*. Nature, 2012. **488**(7410): p. 218-21.
- S8. Ursu, S., et al., Overactive action monitoring in obsessive-compulsive disorder: evidence from functional magnetic resonance imaging. Psychol Sci, 2003. **14**(4): p. 347-53.
- S9. Figee, M., et al., *Dysfunctional reward circuitry in obsessive-compulsive disorder*. Biol Psychiatry, 2011. **69**(9): p. 867-74.
- S10. Greenberg, B.D., D.L. Murphy, and S.A. Rasmussen, *Neuroanatomically based* approaches to obsessive-compulsive disorder. *Neurosurgery and transcranial magnetic stimulation*. Psychiatr Clin North Am, 2000. **23**(3): p. 671-86, xii.
- S11. Ward, H.E., N. Hwynn, and M.S. Okun, *Update on deep brain stimulation for neuropsychiatric disorders*. Neurobiol Dis, 2010. **38**(3): p. 346-53.
- S12. Pittenger, C., et al., *Clinical treatment of obsessive compulsive disorder*. Psychiatry (Edgmont), 2005. **2**(11): p. 34-43.
- S13. Koran, L.M. and H.B. Simpson Guideline Watch (March 2013): Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder. APA Practice Guidelines, 2013.
- S14. *Cochrane Handbook for Systematic Reviews of Interventions*, ed. J.P.T. Higgins and S. Green. 2008: Wiley-Blackwell.
- S15. Goodman, W.K., et al., *The Yale-Brown Obsessive Compulsive Scale. II. Validity.* Arch Gen Psychiatry, 1989. **46**(11): p. 1012-6.
- S16. Goodman, W.K., et al., *The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability.* Arch Gen Psychiatry, 1989. **46**(11): p. 1006-11.

- S17 Koran, L.M., et al., *Practice guideline for the treatment of patients with obsessive-compulsive disorder.* Am J Psychiatry, 2007. **164**(7 Suppl): p. 5-53.
- S18 McGuire, J.F., et al., A Meta-Analysis of Cognitive Behavior Therapy and Medication for Child Obsessive-Compulsive Disorder: Moderators of Treatment Efficacy, Response, and Remission. Depress Anxiety, 2015. 32(8): p. 580-93.
- S19 Carmona, S., et al., *Pediatric OCD structural brain deficits in conflict monitoring circuits: a voxel-based morphometry study.* Neurosci Lett, 2007. **421**(3): p. 218-23.
- S20 Rosenberg, D.R., et al., Frontostriatal measurement in treatment-naive children with obsessive-compulsive disorder. Arch Gen Psychiatry, 1997. **54**(9): p. 824-30.
- S21 O'Neill, J., et al., Glutamate in pediatric obsessive-compulsive disorder and response to cognitive-behavioral therapy: randomized clinical trial. Neuropsychopharmacology, 2017. **42**(12): p. 2414-22.
- S22 Patel, S.R., et al., *Lesion procedures in psychiatric neurosurgery*. World Neurosurg, 2013. **80**(3-4): p. S31 e9-16.
- S23 Rauch, S.L., D.D. Dougherty, and G.R. Cosgrove, *Neurosurgical treatments and deep brain stimulation*, in *Comprehensive Textbook of Psychiatry*. 2005. p. 558-565.
- S24 Ballantine, H.T., Jr., et al., *Stereotaxic anterior cingulotomy for neuropsychiatric illness and intractable pain.* J Neurosurg, 1967. **26**(5): p. 488-95.
- S25 Sheth, S.A., et al., *Limbic system surgery for treatment-refractory obsessive-compulsive disorder: a prospective long-term follow-up of 64 patients.* J Neurosurg, 2013. **118**(3): p. 491-7.
- S26 Leksell, L., A stereotactic apparatus for intracerebral surgery. Acta Chirurgica Scandinavica, 1950. **99**(3): p. 229-233.

- S27 Lopes, A.C., et al., Treatment of resistant obsessive-compulsive disorder with ventral capsular/ventral striatal gamma capsulotomy: a pilot prospective study. J

  Neuropsychiatry Clin Neurosci, 2009. **21**(4): p. 381-92.
- S28 Knight, G., Stereotactic Tractotomy in the Surgical Treatment of Mental Illness. J Neurol Neurosurg Psychiatry, 1965. **28**(4): p. 304-10.
- Nuttin, B., et al., Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. Lancet, 1999. **354**(9189): p. 1526.
- S30 Nuttin, B.J., et al., *Long-term electrical capsular stimulation in patients with obsessive-compulsive disorder*. Neurosurgery, 2003. **52**(6): p. 1263-72; discussion 1272-4.
- Hamani, C., et al., Deep brain stimulation for obsessive-compulsive disorder: systematic review and evidence-based guideline sponsored by the American Society for Stereotactic and Functional Neurosurgery and the Congress of Neurological Surgeons (CNS) and endorsed by the CNS and American Association of Neurological Surgeons. Neurosurgery, 2014. **75**(4): p. 327-33; quiz 333.
- Mian, M.K., et al., *Deep brain stimulation for obsessive-compulsive disorder: past, present, and future.* Neurosurg Focus, 2010. **29**(2): p. E10.
- S33 Luyten, L., et al., *Electrical stimulation in the bed nucleus of the stria terminalis* alleviates severe obsessive-compulsive disorder. Mol Psychiatry, 2016. **21**(9): p. 1272-80.
- van den Munckhof, P., et al., *Active stimulation site of nucleus accumbens deep brain stimulation in obsessive-compulsive disorder is localized in the ventral internal capsule.*Acta Neurochir Suppl, 2013. **117**: p. 53-9.
- S35 Park, H.R., et al., Electrophysiological and imaging evidence of sustained inhibition in limbic and frontal networks following deep brain stimulation for treatment refractory obsessive compulsive disorder. PLoS One, 2019. **14**(7): p. e0219578.

- S36 Lee, D.J., et al., Inferior thalamic peduncle deep brain stimulation for treatment-refractory obsessive-compulsive disorder: A phase 1 pilot trial. Brain Stimul, 2019. **12**(2): p. 344-352.
- S37 Dougherty, D.D., et al., Acute deep brain stimulation changes in regional cerebral blood flow in obsessive-compulsive disorder. J Neurosurg, 2016. **125**(5): p. 1087-1093.
- S38 Figee, M., et al., *Deep brain stimulation induces striatal dopamine release in obsessive-compulsive disorder*. Biol Psychiatry, 2014. **75**(8): p. 647-52.
- S39 Zrinzo, L., et al., Clinical safety of brain magnetic resonance imaging with implanted deep brain stimulation hardware: large case series and review of the literature. World Neurosurg, 2011. 76(1-2): p. 164-72; discussion 69-73.
- Hiss, S., et al., *Intraoperative functional magnetic resonance imaging for monitoring the effect of deep brain stimulation in patients with obsessive-compulsive disorder*. Stereotact Funct Neurosurg, 2015. **93**(1): p. 30-7.
- S41 Boutet, A., et al., Functional MRI Safety and Artifacts during Deep Brain Stimulation: Experience in 102 Patients. Radiology, 2019. **293**(1): p. 174-183.
- S42 Barker, A.T., R. Jalinous, and I.L. Freeston, *Non-invasive magnetic stimulation of human motor cortex*. Lancet, 1985. **1**(8437): p. 1106-7.
- Walsh, V. and A. Cowey, *Transcranial magnetic stimulation and cognitive neuroscience*. Nat Rev Neurosci, 2000. **1**(1): p. 73-9.
- George, M.S., S.H. Lisanby, and H.A. Sackeim, *Transcranial magnetic stimulation:* applications in neuropsychiatry. Arch Gen Psychiatry, 1999. **56**(4): p. 300-11.
- Di Lazzaro, V., et al., Theta-burst repetitive transcranial magnetic stimulation suppresses specific excitatory circuits in the human motor cortex. J Physiol, 2005. 565(Pt 3): p. 945-50.

- Nauczyciel, C., et al., Repetitive transcranial magnetic stimulation over the orbitofrontal cortex for obsessive-compulsive disorder: a double-blind, crossover study. Transl Psychiatry, 2014. 4(9): p. e436.
- S47 Pedapati, E., et al., Neural correlates associated with symptom provocation in pediatric obsessive compulsive disorder after a single session of sham-controlled repetitive transcranial magnetic stimulation. Psychiatry Res, 2015. **233**(3): p. 466-73.
- S48 Gillan, C.M. and T.W. Robbins, *Goal-directed learning and obsessive-compulsive disorder*. Philos Trans R Soc Lond B Biol Sci, 2014. **369**(1655).
- S49 Robbins, T.W., M.M. Vaghi, and P. Banca, *Obsessive-Compulsive Disorder: Puzzles and Prospects*. Neuron, 2019. **102**(1): p. 27-47.
- Kolling, N., et al., *Value, search, persistence and model updating in anterior cingulate cortex.* Nat Neurosci, 2016. **19**(10): p. 1280-5.
- S51 Shenhav, A., M.M. Botvinick, and J.D. Cohen, *The expected value of control: an integrative theory of anterior cingulate cortex function*. Neuron, 2013. **79**(2): p. 217-40.
- S52 Brown, J.W. and W.H. Alexander, Foraging Value, Risk Avoidance, and Multiple Control Signals: How the Anterior Cingulate Cortex Controls Value-based Decisionmaking. J Cogn Neurosci, 2017. **29**(10): p. 1656-1673.
- S53 Botvinick, M., et al., Conflict monitoring versus selection-for-action in anterior cingulate cortex. Nature, 1999. **402**(6758): p. 179-81.
- Shenhav, A., J.D. Cohen, and M.M. Botvinick, *Dorsal anterior cingulate cortex and the value of control*. Nat Neurosci, 2016. **19**(10): p. 1286-91.
- McGovern, R.A. and S.A. Sheth, *Role of the dorsal anterior cingulate cortex in obsessive-compulsive disorder: converging evidence from cognitive neuroscience and psychiatric neurosurgery.* J Neurosurg, 2017. **126**(1): p. 132-147.

- Haber, S.N. and T.E. Behrens, The neural network underlying incentive-based learning: implications for interpreting circuit disruptions in psychiatric disorders. Neuron, 2014.
   83(5): p. 1019-39.
- S57 Remijnse, P.L., et al., *Reduced orbitofrontal-striatal activity on a reversal learning task in obsessive-compulsive disorder*. Arch Gen Psychiatry, 2006. **63**(11): p. 1225-36.
- S58 Gillan, C.M., et al., *Disruption in the balance between goal-directed behavior and habit learning in obsessive-compulsive disorder.* Am J Psychiatry, 2011. **168**(7): p. 718-26.
- S59 Gruner, P. and C. Pittenger, *Cognitive inflexibility in Obsessive-Compulsive Disorder*. Neuroscience, 2017. **345**: p. 243-255.
- Simon, D., et al., Fronto-striato-limbic hyperactivation in obsessive-compulsive disorder during individually tailored symptom provocation. Psychophysiology, 2010. **47**(4): p. 728-38.
- Milad, M.R., et al., *Deficits in conditioned fear extinction in obsessive-compulsive disorder and neurobiological changes in the fear circuit.* JAMA Psychiatry, 2013. **70**(6): p. 608-18.
- Torres, A.R., et al., *Panic Disorder and Agoraphobia in OCD patients: clinical profile and possible treatment implications.* Compr Psychiatry, 2014. **55**(3): p. 588-97.
- S63 Kalanthroff E, A.G., Simpson HB, Research Domain Criteria and Obsessive-Compulsive Disorder: An Oxymoron?, in Obsessive-Compulsive Disorder: Phenomenology, Pathophysiology, and Treatment, C. Pittenger, Editor. 2017, Oxford University Press.
- S64 Cavedini, P., et al., *Decision-making heterogeneity in obsessive-compulsive disorder:*ventromedial prefrontal cortex function predicts different treatment outcomes.

  Neuropsychologia, 2002. **40**(2): p. 205-11.
- Logan, G.D., On the ability to inhibit thought and action: a user's guide to the stop signal paradigm., in Inhibitory processes in attention, memory, and language, D.
   Dagenbach, Carr, T.H., Editor. 1994, Academic Press: San Diego, CA.

- S66 Gillan, C.M., et al., Characterizing a psychiatric symptom dimension related to deficits in goal-directed control. Elife, 2016. 5.
- S67 Menzies, L., et al., *Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited.*Neurosci Biobehav Rev, 2008. **32**(3): p. 525-49.
- S68 Miller, E.K., *The prefrontal cortex and cognitive control.* Nat Rev Neurosci, 2000. **1**(1): p. 59-65.
- Pathak, Y., et al., *The role of electrode location and stimulation polarity in patient response to cortical stimulation for major depressive disorder*. Brain Stimul, 2013. **6**(3): p. 254-60.
- S70 McIntyre, C.C., et al., *Cellular effects of deep brain stimulation: model-based analysis of activation and inhibition.* J Neurophysiol, 2004. **91**(4): p. 1457-69.
- S71 Lehman, J.F., et al., Rules ventral prefrontal cortical axons use to reach their targets: implications for diffusion tensor imaging tractography and deep brain stimulation for psychiatric illness. J Neurosci, 2011. **31**(28): p. 10392-402.
- S72 Chiu, C.H., et al., White matter abnormalities of fronto-striato-thalamic circuitry in obsessive-compulsive disorder: A study using diffusion spectrum imaging tractography. Psychiatry Res, 2011. **192**(3): p. 176-82.
- S73 Setsompop, K., et al., *Pushing the limits of in vivo diffusion MRI for the Human Connectome Project.* Neuroimage, 2013. **80**: p. 220-33.
- Nanda, P., et al., *Connectivity-based parcellation of the anterior limb of the internal capsule*. Hum Brain Mapp, 2017. **38**(12): p. 6107-6117.
- S75 Safadi, Z., et al., Functional Segmentation of the Anterior Limb of the Internal Capsule: Linking White Matter Abnormalities to Specific Connections. J Neurosci, 2018. **38**(8): p. 2106-2117.

- S76 Rodriguez-Romaguera, J., F.H. Do Monte, and G.J. Quirk, *Deep brain stimulation of the ventral striatum enhances extinction of conditioned fear*. Proc Natl Acad Sci U S A, 2012. **109**(22): p. 8764-9.
- S77 Riva-Posse, P., et al., *Defining critical white matter pathways mediating successful subcallosal cingulate deep brain stimulation for treatment-resistant depression.* Biol Psychiatry, 2014. **76**(12): p. 963-9.
- S78 Riva-Posse, P., et al., A connectomic approach for subcallosal cingulate deep brain stimulation surgery: prospective targeting in treatment-resistant depression. Mol Psychiatry, 2018. **23**(4): p. 843-849.
- S79 Vaghi, M., et al., Specific frontostriatal circuits for impaired cognitive flexibility and goal-directed planning in obsessive-compulsive disorder: evidence from resting-state functional connectivity. Biol Psychiatry, 2017. **81**(8): p. 708-717.
- S80 Chamberlain, S., et al. *Orbitofrontal dysfunction in patients with obsessive-compulsive disorder and their unaffected relatives.* Science, 2008. **321**(5887): p. 421-422.
- Remijnse, P., et al., *Reduced orbitofrontal-striatal activity on a reversal learning task in obsessive-compulsive disorder.* Arch Gen Psychiatry, 2006. **63**(11): p. 1225-1236.